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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,604	03/28/2006	Jo Klaveness	PN0369	6866
36335 7590 12/11/2008 GE HEALTHCARE, INC. IP DEPARTMENT 101 CARNEGIE CENTER PRINCETON, NJ 08540-6231				
EXAMINER				
SCHLIENTZ, LEAH H				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/573,604

Applicant(s)

KLAVENESS ET AL.

Examiner

Leah Schlientz

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SG/US)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an optical imaging contrast agent with an affinity for an abnormally expressed biological target associated with endometrioses of formula I, V-L-R, wherein V is one or more vector moieties having affinity for an abnormally expressed target in endometriosis, L is a linker moiety or a bond and R is one or more reporter moieties detectable in in vivo optical imaging, and wherein the contrast agent has a molecular weight below 10000 Daltons. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed composition. For example, a vast number of potential "vector moieties having an affinity for an abnormally expressed target in endometriosis" may be found in the art to be capable of having the claimed function. Applicant has identified in the instant specification a diverse variety of targets for which the vector may have affinity including

VEGF, integrins, estrogen receptors, progesterone receptors, ICAM-1, cathepsin H, oncogenes, interleukin-6, etc. (see paragraphs 0011-0085 of the instant specification). Such targets are widely varying in structure and would have an almost unlimited number of potential vectors which may have affinity thereto. The vectors themselves may be almost unlimited including various peptide sequences, small molecules, antibodies, nucleic acid sequences, etc. It is clear that Applicant had possession of such a specific formulations at the time of filing as identified in compounds I-VI of the specification and the Examples, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed contrast agent, one would have to determine the type of vector having affinity to which out of an extremely large number of targets to conjugate to which out of an almost unlimited number of potential optical imaging moieties to be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties. One would have to select which portions of which molecules would be suitable to be conjugated to the others and on what positions of the molecules with various substituents. Applicant's limited disclosure of a particular compound which has the claimed functional properties does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the

agent does, rather than what it is. See MPEP 2163 and *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406.

Claim Rejections - 35 USC § 102

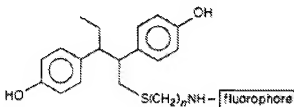
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13, 16-18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Fevig *et al.* (*J. Med. Chem.*, 1987, 30, p. 156-165).

Fevig discloses thioether-linked norhexestrol-fluorophore conjugates as shown in Table III, having high estrogen receptor binding affinity and favorable fluorescence quantum yield. The compounds are intended for use in optical imaging of tumor, e.g. such as in breast cancer (see page 156, Table III, page 162).



Regarding the limitation of the instant claims wherein the optical contrast agent has an "affinity for an abnormally expressed biological target associated with endometriosis," it is noted that the estrogen receptor is associated with endometriosis, as evidenced by instant claim 16. The intended use of the vector as "having affinity for

an abnormally expressed target in endometriosis" has not been given patentable weight to distinguish over Fevig because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Fevig discloses compounds that are the same as those claimed (e.g. having V-L-R, wherein V is a vector for estrogen receptor, L is thioether, and R is a fluorophore (NBD)), they would be capable of performing the intended use, as claimed.

Claims 13, 17-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Jallad *et al.* (US 2003/0162234).

Jallad discloses methods of differentiating tumors from healthy cells in tissue including the steps of providing a marker-folate conjugate, placing the marker folate conjugate in contact with the tissue and viewing the tissue (abstract). Such compounds include folate-fluorescein and folate-indocyanine, as in Figure 3a and 3b (paragraph 0016-0017). Tumors that regularly express the folate receptor include cancer of the ovary, breast, kidney, lung and endometrium (paragraph 0033). In many cases, patients must undergo a second-look surgery to determine whether relapse has occurred. In this situation, an optical method that could readily distinguish cancer from non-cancer is beneficial (paragraph 0052). Regarding instant claim 20, Jallad teaches a PBS solution as excipient (paragraph 0038).

Claims 13-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Weissleder *et al.* (US 2003/0044353).

Weissleder discloses activatable imaging probes that includes a chromophore attachment moiety and one or more chromophores, such as near-infrared chromophores, chemically linked to the chromophore attachment moiety so that upon activation of the imaging probe the optical properties of the plurality of chromophores are altered. The probe optionally includes protective chains or chromophore spacers, or both. Also disclosed are methods of using the imaging probes for optical imaging (see abstract). A number of specific peptide substrates including cathepsin B-specific peptide substrates, MMP substrates, thrombin substrates and others are included in the probes of the present invention (see, e.g., Table 2). Examples of cathepsin B-specific substrates include RRK(FITC)C-NH₂, etc. An example of a MMP substrate is Gly-Pro-Leu-Gly-Val-Arg-Gly-Lys(FI-TC)-Cys-NH₂ (paragraph 0089). Cathepsin S is also disclosed as a target (Table 2). Exemplary chromophores include cyanines (cy5.5, cy5, cy7) (Table 1 and Examples). Pharmaceutical compositions include sterile injectable solutions including isotonic saline, etc. (paragraph 0128-0129). See also Examples.

Regarding the limitation of the instant claims wherein the optical contrast agent has an "affinity for an abnormally expressed biological target associated with endometrioses," it is noted that cathepsin s is associated with endometriosis, as evidenced by instant claim 16. It is noted that MMP substrates are also associated with endometriosis, as evidenced by Applicant's specification at paragraph 0014. The

intended use of the vector as "having affinity for an abnormally expressed target in endometriosis" has not been given patentable weight to distinguish over Weissleder because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Weissleder discloses compounds that are the same as those claimed, they would be capable of performing the intended use, as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fevig *et al.* (*J. Med. Chem.*, 1987, 30, p. 156-165) in view of Wallace *et al.* (US 6,096,874).

Fevig discloses thioether-linked norhexestrol-fluorophore conjugates as shown in Table III, having high estrogen receptor binding affinity and favorable fluorescence quantum yield. The compounds are intended for use in optical imaging of tumor, e.g. such as in breast cancer (see page 156, Table III, page 162).

Fevig does not specifically recite imaging of endometriosis with the compounds.

However, in addition to breast cancer, estrogen receptor-rich tissues may also be be found in breast, ovarian, uterine and brain tissue.

For example, Wallace teaches tamoxifen derivatives having a tamoxifen derivative conjugated to a DTPA diagnostic moiety. The compounds are used as highly specific imaging agents for estrogen-receptor rich tissues (abstract). They may be used in imaging of estrogen receptors, for example in breast, ovarian, uterine and brain tissues and may therefore be useful in the diagnosis of estrogen receptor positive cancers, meningiomas and endometriosis.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the compounds of Fevig for imaging of additional tumor tissues in addition to breast tumor, such as endometriosis, when the disclosure of Fevig is taken in view of Wallace. Both Fevig and Wallace are directed to diagnostic imaging of tumor or cancer using diagnostic moieties conjugated to targeting agents directed to estrogen receptor. Since Wallace teaches that estrogen receptor rich tissues include both both

breast and uterine tissue, and teaches that compounds having affinity for estrogen receptor may be useful for imaging estrogen receptor positive cancers, such as endometriosis, one would have had a reasonable expectation of success in using Fevig's compounds having high affinity for estrogen receptor for imaging endometriosis.

Claims 13-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissleder *et al.* (US 2003/0044353), in view of Schneider *et al.* (US 6,387,629).

Weissleder discloses activatable imaging probes that includes a chromophore attachment moiety and one or more chromophores, such as near-infrared chromophores, chemically linked to the chromophore attachment moiety so that upon activation of the imaging probe the optical properties of the plurality of chromophores are altered. The probe optionally includes protective chains or chromophore spacers, or both. Also disclosed are methods of using the imaging probes for optical imaging (see abstract). Cathepsin S is also disclosed as a target (Table 2). Exemplary chromophores include cyanines (cy5.5, cy5, cy7) (Table 1 and Examples). Pharmaceutical compositions include sterile injectable solutions including isotonic saline, etc. (paragraph 0128-0129). See also Examples.

Weissleder does not specifically recite optical imaging of endometriosis with his probes.

Schneider discloses that cathepsin s expression is up-regulated in endometriotic tissue and provides methods of diagnosing endometriosis by detecting up-regulation of cathepsin s gene product and methods of treating endometriosis (abstract). Kits are

included for diagnosing, prognosing and monitoring the course of endometriosis (column 22, lines 1-10). See SEQ ID 3 or 4 which are capable of detecting cathepsin S mRNA (column 32, lines 38+). Fluorescent probes are also disclosed, as are cleavable products (column 27).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the compounds of Weissleder for imaging of endometriosis, when the disclosure of Weissleder is taken in view of Schneider. Since Weissleder teaches that his activateable probes may be administered for tumor imaging, including probes having affinity for cathepsin s, it would have been obvious that such a probe would be useful in imaging endometriosis because Schneider teaches that cathepsin s is upregulated in endometrial tissue and that detection of cathepsin s is useful in methods of diagnosing endometriosis (column 10, lines 18-26).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/573,606, 10/582,679, 10/582,680, 10/582,842, and 10/582,893. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to an optical contrast agent with an affinity for an abnormally expressed biological target associated with endometriosis of formula V-L-R, wherein V is one or more vector moieties having affinity for abnormally expressed target in endometriosis. The claims of the '606, '679, '680, '842 and '893 applications are drawn to optical contrast agents having formula V-L-R, wherein V has an affinity for abnormally expressed targets associated with colorectal cancer, oesophageal cancer, atherosclerotic plaque, prostate cancer, and lung cancer, respectively. The specifications of the instant application and those of the 606, '679, '680, '842 and '893 applications define that vectors having affinity for various abnormally expressed biological targets may be the same (e.g. vectors for angiogenesis targets, adhesion molecules, estrogen receptors, metalloproteinases, e-cadherin, cathepsin B, cox-2, etc.). The contrast agents are the same and should be capable of the same functions. Accordingly the claims are overlapping in scope and are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618
LHS